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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 7/16, 7/26, 35/78 — A1

(11) International Publication Number: **WO 97/16159**

(43) International Publication Date: 9 May 1997 (09.05.97)

(21) International Application Number: PCT/US96/16948

(22) International Filing Date: 23 October 1996 (23.10.96)

(30) Priority Data:
08/550,045 30 October 1995 (30.10.95) US

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(81) Designated States: AL, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KR, LK, LR, LS, LT, LV, MG, MK, MN, MW, MX, NO, NZ, PL, RO, SD, SG, SI, SK, TR, TT, UA, UG, UZ, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ENHANCED ANTI-INFLAMMATORY ORAL COMPOSITION CONTAINING H_2 RECEPTOR ANTAGONIST AND ANTIMICROBIAL OILS

(57) Abstract

An anti-inflammatory oral composition that is effective in preventing and treating gingivitis and periodontitis containing an H_2 receptor antagonist and antimicrobial oils. A method of preventing or treating inflammations in the oral cavity by applying an effective amount of the anti-inflammatory oral composition to the oral cavity is also provided.

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TITLE

ENHANCED ANTI-INFLAMMATORY ORAL COMPOSITION CONTAINING H_2 RECEPTOR ANTAGONIST AND ANTIMICROBIAL OILS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to an oral composition containing an H_2 receptor antagonist and antimicrobial oils that is effective in preventing and treating gingivitis and periodontitis.

Description of the Background Art

Inflammations in the oral cavity such as gingivitis and periodontitis are usually caused by dental plaque that contains bacteria harmful to gums. To reduce dental plaque, antimicrobial oils, such as essential oils, have been used for years in antiseptic and antiplaque mouthwash solutions. For example, LISTERINE® brand antiseptic mouthwash has been marketed since 1881, and contains the essential oils thymol, menthol, eucalyptol, and methyl salicylate. More recently, essential oils have been included in formulations of toothpaste.

U.S. Patent No. 1,526,940 teaches a toothpaste with the germicide ammonium ichthyol sulphonate with high amounts of thymol, menthol, eucalyptol, methyl salicylate, and peppermint oil as flavorants and taste-masking ingredients.

U.S. Patent No. 3,164,524 to Fand et al. teaches an oral antiseptic comprising 2, 2'-thiobis-(4,6-dichlorophenol), boric acid, methyl salicylate, thymol, menthol, and eucalyptol.

U.S. Patent No. 5,094,843 to Mazzanobile et al. teaches an anti-plaque, anti-gingivitis toothpaste with a fluorine source, and a specific range of thymol, menthol, methyl salicylate and eucalyptol.

European Patent Application 04974776 to Colgate-Palmolive Co. teaches an anti-plaque oral composition, including a toothpaste, with triclosan. The anti-plaque activity of the triclosan is increased by essential oils such as eucalyptol, thymol, methyl salicylate, and menthol.

Histamine H_2-receptor antagonists have been taught as capable of treating gingivitis and periodontitis. For example, U.S. Patent No. 5,294,433 to Singer et al. discloses a toothpaste composition containing a selective histamine H_2 receptor antagonist compound.

SUMMARY OF THE INVENTION

The present inventors have discovered an oral composition containing a histamine H_2 receptor antagonist and antimicrobial oils that is particularly effective in preventing and treating inflammations in the oral cavity, such as gingivitis and periodontitis.

More specifically, the present invention provides an anti-inflammatory oral composition comprising an H_2 receptor antagonist and antimicrobial oils. The present invention also provides a method of preventing or treating inflammations in the oral cavity which comprises applying thereto an effective amount of a composition comprising an H_2 receptor antagonist and antimicrobial oils.

DETAILED DESCRIPTION OF THE INVENTION

Histamine H_2-receptor antagonists are known as effective agents for treating conditions that benefit from the lowering of gastric acidity, such as duodenal and gastric ulceration, reflux esophagitis and Zollinger-Ellison syndrome. The present inventors have discovered that when a histamine H_2-receptor antagonist is administered together with antimicrobial oils in an oral composition, anti-inflammatory conditions in the oral cavity such as gingivitis and periodontitis can also be effectively prevented and treated. Examples of suitable histamine H_2-receptor antagonists that can be used in the present invention include ranitidine, cimetidine, nizatidine, and famotidine. The preferred H_2-receptor antagonist for use in this invention is ranitidine. The chemical name for ranitidine is N-[2-[[[5-(dimethylamino) methyl-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine. This compound and its physiologically acceptable salts are described and claimed in U.S. Patent No. 4,128,658. A particular crystalline form of ranitidine hydrochloride is described and claimed in U.S. Patent No. 4,521,431.

The H_2-receptor antagonist may be employed in the oral composition according to the present invention in the form of either its free base or a physiologically acceptable salt. Such salts include salts with inorganic or organic acids such as the hydrochloride, hydrobromide, sulphate, acetate, maleate, succinate, fumarate,

and ascorbate salts. A particularly preferred salt for use according to the present invention is the hydrochloride salt.

The H_2-receptor antagonist is employed in the oral composition of this invention in an amount which is effective to prevent or treat inflammations in the oral cavity, and preferably in an amount of from about 0.01% to about 5%, and most preferably from about 0.025 % to about 0.3% by weight, based on the total weight of the oral composition.

Essential oils may be used as the antimicrobial oils in the present invention. Essential oils are volatile aromatic oils which may be synthetic or may be derived from plants by distillation, expression or extraction, and which usually carry the odor or flavor of the plant from which they are obtained. In the oral composition of this invention, antiseptic activity is provided by these essential oils. Some of these essential oils also act as flavoring agents. The essential oils useful in this invention include but are not limited to thymol, menthol, methyl salicylate (wintergreen oil), eucalyptol, carvacrol, camphor, anethole, carvone, eugenol, isoeugenol, limonene, osimen, n-decyl alcohol, citronel, α-salpineol, methyl acetate, citronellyl acetate, methyl eugenol, cineol, linalool, ethyl linalaol, safrola vanillin, spearmint oil, peppermint oil, lemon oil, orange oil, sage oil, rosemary oil, cinnamon oil, pimento oil, laurel oil, cedarleaf oil, and clove oil, and mixtures thereof. The essential oils are used in this invention generally in amounts effective to provide an antiseptic (antimicrobial) function in the oral cavity. Those skilled in the art know how much of the essential oils are required to provide this function. Typically, the essential oils may be included in the oral composition of the present invention in an amount of from about 0.01% to about 2%, preferably in an amount of from about 0.1% to about 1%, and most preferably in an amount of from about 0.2% to about 0.5% by weight, based on the total weight of the oral composition.

Thymol, also known by the chemical formula 5-methyl 2-(1-methylethyl) phenol, is obtained from the essential oil of Thymus vulgaris Labiatae and Monarda punctata Labiatae. Thymol is a white crystalline powder with an aromatic odor and taste. It is soluble in organic solvents but only slightly soluble in deionized water. Thymol may be employed in the oral composition of this invention in an amount of from about 0.001% to about 2%, preferably in an amount of from about 0.05% to about 1%, and most preferably in an amount of from about 0.01% to about 0.5% by weight, based on the total weight of the oral composition.

Menthol is isolated principally from the oil of Mentha arvensis. In its commercial form, menthol is available as L-menthol crystals obtained from a process involving cooling of the oil. Fractional distillation of peppermint oil which usually contains from about 40% to about 65% menthol represents another important source of menthol. Synthetic sources of L-menthol are also available. Menthol may be employed in the oral composition of the present invention in an amount of from about 0.001% to about 2%, preferably in an amount of from about 0.005% to about 1%, and most preferably in an amount of from about 0.01% to about 0.5% by weight, based on the total weight of the oral composition.

Eucalyptol, another essential oil with antiseptic properties, is derived from the eucalyptus tree. Having a camphoraceous odor and cooling taste, this essential oil is often combined with other essential oils such as menthol in confection formulations to impart medicinal effect. Combinations of menthol and eucalyptol are widely used. Particularly preferred uses of the menthol-eucalyptol combination include, according to the present invention, dentifrices such as toothpastes or dental gels. Eucalyptol may be employed in the oral composition of the present invention in an amount of from about 0.001% to about 2%, preferably in an amount of from about 0.005% to about 1%, and

most preferably in an amount of from about 0.01% to about 0.5% by weight, based on the total weight of the oral composition.

Methyl salicylate is the main ingredient in many essential oils, constituting about 99% of oil of wintergreen (Gaultheria procumbens) and sweet birch (Betula lenta). Methyl salicylate, which has a distinctive refreshing aroma, is used widely in mouthwashes, chewing gums and other oral and pharmaceutical preparations. Methyl salicylate may be employed in the oral composition of the present invention in an amount of from about 0.001% to about 2%, preferably in an amount of from about 0.005% to about 1%, and most preferably in an amount of from about 0.01% to about 0.5% by weight, based on the total weight of the oral composition.

The oral composition of this invention may contain the following essential oils in the stated percentages by weight: (a) thymol from about 0.001% to about 2%; (b) menthol from about 0.001% to about 2%; (c) eucalyptol from about 0.001% to about 2%; and (d) methyl salicylate from about 0.001% to about 2%; based on the total weight of the oral composition.

In the preferred embodiment, the oral composition of the present invention may contain the following essential oils in the stated percentages by weight: (a) thymol from about 0.005% to about 1.0%; (b) menthol from about 0.005% to about 1.0%; (c) eucalyptol from about 0.005% to about 1.0%; and (d) methyl salicylate from about 0.005% to about 1.0%; based on the total weight of the oral composition.

In the most preferred embodiment, the oral composition of the present invention may contain the following essential oils in the stated percentages by weight: (a) thymol from about 0.01% to about 0.5%; (b) menthol from about 0.01% to about 0.5%; (c) eucalyptol from about 0.01% to about 0.5%; and (d) methyl

salicylate from about 0.01% to about 0.5%; based on the total weight of the oral composition.

The oral composition of this invention may also contain an anticaries agent. Suitable anticaries agents include fluoride-releasing compounds that may be fully or slightly water-soluble, and are characterized by their ability to release fluoride ions or fluoride-containing ions in water and by their lack of reaction with other components in the composition. Typical fluoride-releasing compounds are inorganic fluoride salts such as water-soluble alkaline earth metal, alkali metal, and heavy metal fluoride salts. Sodium monofluorophosphate, sodium fluoride, stannous fluoride and mixtures thereof are preferred.

The amount of fluoride-releasing compound present in a preferred embodiment of this invention depends upon the type of fluoride-releasing compound employed, the solubility of the fluoride-releasing compounds, and the formulation of the oral composition. The fluoride-releasing compound must be used in a nontoxic amount. In general, the fluoride-releasing compound, when used, will be present in an amount by weight of up to about 0.002%, preferably from about 0.0001% to about 0.02%, and most preferably from about 0.0005% to about 0.003%, based on the total weight of the oral composition so as to release 800-1500 parts per million ("ppm") F^-.

The most preferred fluoride-releasing compound in the oral composition of the invention is sodium monofluorophosphate at a concentration by weight, based on the total weight of the composition, of from about 0.0001% to about 0.02%, more preferably about 0.0005% to about 0.005%, or most preferably, about 0.003%.

The pH for the preferred embodiment according to the present invention is from about 4.0 to about 7.0. A pH between about 5.5 and about 7.5 has been found to partially reduce the antiseptic activity of the oral composition.

The pH of the oral composition may be adjusted to below about 5.5 using suitable food or pharmaceutical grade acidifiers. These could include, but are not limited to, one or a combination of the following: phosphoric acid, benzoic acid, citric acid, or other tricarboxylic acids, and the like. The most preferred acidifiers in the present invention include a mixture of phosphoric acid, monobasic sodium phosphate, dibasic sodium phosphate, and benzoic acid. In that mixture, phosphoric acid is used in an amount of from about 0.01% to about 1.0%, preferably from about 0.02% to about 0.5%, and most preferably from about 0.1% to about 0.3%; monobasic sodium phosphate is used in an amount of from about 0.01% to about 1.0%, preferably from about 0.2% to about 0.5%, and most preferably from about 0.01% to about 0.3%; dibasic sodium phosphate is used in an amount of from about 0.01% to about 1.0%, preferably from about 0.02% to about 0.05%, and most preferably from about 0.1% to about 0.3%; and benzoic acid is used in an amount of from about 0.01% to about 1.0%, preferably from about 0.02% to about 0.5%, and most preferably from about 0.1% to about 0.3%; all percentages being by weight based on the total weight of the oral composition. The exact amount of acidifier added will depend on the final pH and buffer capacity desired.

The pH of the products may also be buffered with salts of the acids in question. Common buffer systems include phosphoric acid and sodium phosphate salts, or citric acid and sodium citrate. Suitable buffers for use in this invention include citric acid-sodium citrate, phosphoric acid-sodium phosphate, sodium monobasic phosphate-sodium dibasic phosphate, acetic acid-sodium acetate, and benzoic acid and benzoate in amounts up to about 1.0%, preferably from about 0.2% to

about 0.5%, and most preferably from about 0.1% to about 0.3%, by weight based on the total weight of the oral composition.

In the preferred embodiment of this invention, the oral composition includes an oral vehicle which may be any spray or foam, conventional solid, semisolid or liquid system, including a spray or foam, that provides a composition suitable for oral administration, especially topical administration to the tissues where inflammation occurs, such as the gums and periodontal tissues. The oral vehicle typically contains conventional additives including but not limited to humectants, binders, thickeners, surfactants, preservatives, sweeteners, flavors, colors, glycerin, and a buffer. These additives are present in amounts that do not interfere with the antiseptic and anti-inflammatory properties of the oral composition of the present invention.

Surfactants or surface active agents are organic compounds which reduce surface tension between liquids and aid in the dispersion of a composition throughout the oral cavity. A surfactant for possible use in the present invention includes anionic, nonionic, and amphoteric surfactants. The oral composition of the present invention may contain surfactants in amounts by weight up to about 2%; preferably from about 0.1% to about 1%, and most preferably from about 0.1% to about 0.5%, based on the total weight of the oral composition.

The most preferred surfactants are anionic. These anionic surfactants include but are not limited to sodium lauryl sulfate, sodium lauroyl sarcosinate, sodium methyl cocoyl taurate, and disodium lauryl sulfosuccinate.
In the most preferred embodiment the surfactant is the anionic surfactant sodium lauryl sulfate.

Amphoteric surfactants have the capacity to behave as either an acid or a base and include quaternized imidazole derivatives useful in the present invention. Preferred amphoteric surfactants include long chain (alkyl) amino-alkylene aklylated amine derivatives, also known as MIRANOL®, manufactured by Rhone-Poulenc, Cranbury, New Jersey.

Sweeteners well known in the art, including natural and artificial sweeteners, may be used. The sweetener may be selected from a wide range of materials including naturally occurring water-soluble sweeteners, artificial water-soluble sweeteners and modified water-soluble sweeteners derived from naturally occurring water-soluble sweeteners. Artificial water-soluble sweeteners include, but are not limited to, soluble saccharin salts, e.g., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide, the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (Acesulfame-K), the free acid form of saccharin, and the like; dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, e.g., L-aspartyl-L-phenylalanine methyl ester (aspartame) and materials described in U.S. Pat. No. 3,492,131, L-alpha-aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate (Alitame), methyl esters of L-aspartyl-L-phenylglycerine, and L-aspartyl-L-2,5-dihydrophenylglycine, L-aspartyl-2,5-dihydro-L-phenylalanine; L-aspartyl-L-(1-cyclohexene)-alanine, and the like. Naturally occurring water-soluble sweeteners include, but are not limited to, sugar alcohols, including sorbitol as 70% sorbitol solution, mannitol, xylitol, maltitol, hydrogenated starch hydrolysates and mixtures thereof.

Water-soluble sweeteners derived from naturally occurring water-soluble sweeteners include, but are not limited to, chl rinated derivatives of sucrose, known, for example, under the product designation of Sucralose®; and protein-based sweeteners such as thaumaoccous danielli (Thaumatin I and II).

Sorbitol solution supplies sweetness and body to the composition and gives a desirable mouth feel. Sorbitol solution also enhances flavor, prevents harsh taste and provides a fresh and lively sensation in the mouth. It also prevents caking of the dentifrice.

In general, an effective amount of sweetener is utilized to provide the level of sweetness desired in any particular embodiment of the oral compositions according to the present invention. This amount will vary with the sweetener selected and the final oral hygiene product. The amount of sweetener normally present is from about 0.01% to about 0.1% by weight based on the total weight of the oral composition.

The flavors which may be used in the invention include natural and artificial flavors known in the art. Suitable flavors include, but are not limited to, mints such as peppermint, citrus flavors such as orange and lemon, artificial vanilla, cinnamon, various fruit flavors, and the like. Anethole (or anise camphor, p-propenyl anisole), a flavor constituent of anise and fennel oils used widely as a flavoring agent and antiseptic, was found useful in masking the harsh taste of thymol. The flavors are preferably artificial.

The amount of flavor is normally a matter of preference subject to such factors as the type of final oral composition, the individual flavor employed, and the strength of flavor desired. The flavors are preferably utilized in total amounts of from about 0.005% to about 1.0% by weight, based on the total weight of the oral composition.

Coloring agents may be used in this invention in amounts effective to produce an oral composition of a desired color. These coloring agents may be incorporated in amounts up to about 0.1% by weight based on the total weight of the oral composition of the present invention. The coloring agents may also

include natural food colors and dyes suitable for food, drug and cosmetic applications. These coloring agents are known as FD&C dyes and lakes. The materials acceptable for the foregoing uses are preferably water-soluble. Illustrative nonlimiting examples include the indigoid dye known as FD&C Blue No. 1, and D&C Yellow No. 10. A full recitation of all FD&C colorants and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Edition, in volume 5 at pages 857-884. A preferred opacifier, titanium dioxide, may be incorporated in an amount up to about 2.0%, preferably less than about 1.0%, and most preferably less than about 0.1%, by weight based on the total weight of the oral composition.

Suitable humectants may be used in this invention, including sorbitol, as 70% sorbitol solution, mannitol, other polyols, hydrogenated starch hydrolysates, mixtures thereof, and the like. Humectants may be present in amounts from about 5% to about 50% by weight based on the total weight of the oral composition.

Suitable abrasive substances for use in this invention include hydrated silica, calcium carbonate, calcium pyrophosphate, dicalcium phosphate dihydrate, or alkali metal meta-phosphates. Silica abrasives in the oral composition according to this invention may include among others, ZEODENT® (113), manufactured by J.M. Huber Corp. and SYLOID® or SYLODENT® manufactured by W.R. Grace Co. These polishing agents may be used in amounts by weight up to about 25%, preferably in amounts from about 15% to about 20%, and most preferably from about 5% to about 15%, based on the total weight of the oral composition.

The oral composition of this invention may also include binders or gelling agents to give the products their characteristic consistency. Gelling agents such as hydroxyethyl cellulose, carboxymethyl cellulose, methyl cellulose, xanthan

gum, gelling silicas, and the like may be used singly or in combination. The preferred gelling system is a mixture of carboxy methyl cellulose, xanthan gum and gelling silica. Gelling agents may be used in amounts by weight of from about 1.0% to about 10%, preferably from about 2% to about 5%, and most preferably from about 2% to about 4%, based on the total weight of the oral composition.

The oral composition of this invention may also contain a desensitizing agent such as strontium chloride, potassium nitrate or sodium citrate-citric acid, which may be used in an amount by weight of from about 0.1% to about 15%, based on the total weight of the total composition.

Suitable preservatives in this invention include benzoic acid, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbic acid, methyl paraben, propyl paraben, tocopherols and mixtures thereof. Preservatives when used are generally present in amounts by weight up to about 2%, and preferably from about 0.05% to about 0.5% based on the total weight of the oral composition.

The oral composition according to the present invention may be made by any known methods into forms suitable for oral topical administration. These forms include toothpaste, tooth gels, tooth powders, mouthwashes, mouthsprays, and the like. Preferably, the oral composition is in the form of a toothpaste or gel.

While the present invention has been described with respect to what is presently considered to be the preferred embodiments, it is to be understood that the invention is not limited to the disclosed embodiments. To th contrary, the invention is intended to cover various modifications and equivalent formulations included within the spirit and scope of the appended claims. The scope of the

following claims is to be accorded the broadest interpretation so as t encompass all such modifications and equivalent formulations and functions.

WHAT IS CLAIMED IS:

1. An anti-inflammatory oral composition containing an H_2 receptor antagonist and antimicrobial oils.

2. The anti-inflammatory oral composition according to Claim 1, wherein said H_2 receptor antagonist is selected from a group consisting of ranitidine, cimetidine, nizatidine, and famotidine, and physiologically acceptable salts thereof.

3. The anti-inflammatory oral composition according to Claim 2, wherein said H_2 receptor antagonist is ranitidine or a physiologically acceptable salt thereof.

4. The anti-inflammatory oral composition according to Claim 1, wherein said composition is buffered to a pH range of from about 3.0 to about 5.5.

5. The anti-inflammatory oral composition according to Claim 1, wherein said antimicrobial oils are selected from the group consisting of thymol, methyl salicylate, menthol eucalyptol, spearmint oil, cinnamon oil, clove oil, rosemary oil, and peppermint oil.

6. The anti-inflammatory oral composition according to Claim 5, wherein said antimicrobial oils comprise thymol, methol, methyl salicylate, and eucalyptol.

7. The anti-inflammatory oral composition according to Claim 1, further comprising one or more fluoride-releasing compounds.

8. The anti-inflammatory oral composition according to Claim 7, wherein said fluoride-releasing compound is selected from the group consisting of monofluorophosphate, alkali metal fluoride, stannous fluoride, aluminum monofluorophosphate, aluminum difluorophospate, and mixtures thereof.

9. A method for treating inflammations in the oral cavity, which comprises applying thereto an effective amount of a composition comprising an H_2 receptor antagonist and antimicrobial oils.

10. The method according to Claim 9, wherein said H_2 receptor antagonist is selected from a group consisting of ranitidine, cimetidine, nizatidine, and famotidine, and physiologically acceptable salts thereof.

11. The method according to Claim 10, wherein said H_2 receptor antagonist is ranitidine or a physiologically acceptable salt thereof.

12. The method according to Claim 9, wherein said composition is buffered to a pH range of from about 4.0 to about 7.0.

13. The method according to Claim 9, wherein said antimicrobial oils are selected from the group consisting of thymol, methyl salicylate, menthol eucalyptol, spearmint oil, cinnamon oil, clove oil, rosemary oil, and peppermint oil.

14. The method according to Claim 13, wherein said antimicrobial oils comprise thymol, ethol, methyl salicylate, and eucalyptol.

15. The method according to Claim 9, further comprising one or more fluoride-releasing compounds.

16. The method according to Claim 15, wherein said fluoride-releasing compound is selected from the group consisting of monofluorophosphate, alkali metal fluoride, stannous fluoride, aluminum monofluorophosphate, aluminum difluorophospate, and mixtures thereof.

INTERNATIONAL SEARCH REPORT

'n' ional Application No
PCT/US 96/16948

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/16 A61K7/26 A61K35/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 294 433 A (SINGER ET AL.) 15 March 1994 cited in the application see examples 5-8	1-16
A	US 5 364 616 A (SINGER ET AL.) 15 November 1994 see claims 1,16-27; examples 5-8	1-16
A	WO 92 04893 A (SMITHKLINE BEECHAM CORPORATION) 2 April 1992 see examples 2-4	1-16
A	WO 94 08560 A (GLAXO GROUP) 28 April 1994 see the whole document	1-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Fischer, J.P.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 18939 A (WARNER-LAMBERT COMPANY) 1 September 1994 see the whole document	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/16948

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